REMARKS

The following remarks are being submitted as a full and complete response to the Office Action dated October 10, 2005, in view of which the Examiner is respectfully requested to give due reconsideration to all outstanding rejections and/or objections, that they be withdrawn, and to indicate the allowability of the claims, and to pass this case to issue.

Applicants gratefully acknowledge the Examiner's withdrawal of objections to the title of this invention.

Status of the Claims

Claims 3-13 are pending in the application. No claims have been amended.

Rejection under 35 U.S.C. §112, 1st paragraph

Claims 3 – 13 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. The Examiner asserts that the claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and /or use the invention.

The Examiner further asserts that Applicants have not set forth the starting materials and the reaction conditions such that one of skill in the art can practice the claimed invention to the full extent of the claims' scope without undue experimentation.

The Examiner, citing Zhang et al., (Bioinformatics, vol 19, No. 1, 2003, page 14) and Chan (US 2002/0119455) further asserts that the claimed device clearly relates to performing nucleic acid hybridization reactions as well as performing amplification reactions (e.g., PCR); both of which are recognized in the art as being problematic and require greater levels of enabling disclosure.

The Examiner further asserts that Carrico (US Patent 5, 200, 313) recognizes a non-exclusive list of variables that affect a hybridization reaction including: the purity of the nucleic acid preparation; base compositions of the probe; length of homologous base sequence; ionic strength; incubation temperature; nucleic acid concentration and incubation time; denaturing reagents; volume exclusion agents; repeated washes or rinses etc.; and that Applicants have given limited guidance as to those variables.

Applicants respectfully disagree with the Examiner and hereby traverse as follows:

The Examiner's enablement standard pursuant to 35 U.S.C. § 112, first paragraph, is improper and far exceeds the legal requirements for patentability.

Applicants respectfully ask the Examiner to tailor his considerations under 35 U.S.C. 112, first paragraph, to what the Applicants have distinctly described, enabled and claimed. Applicant have claimed a hybridization device comprising specifically enumerated embodiments and have described said device such that a skilled artisan in the art can make and use the full scope of the invention without undue experimentation. The requirement by Examiner of disclosures not reasonably tailored to enable that which is claimed is clearly improper.

In prior Office Actions, the Examiner so raised the bar under 35 U.S.C. § 112, first paragraph, to require descriptions of the particular biopolymeric species to be hybridized, including sequence listings of proteins and nucleic acids. In the current Office Action, the Examiner is requiring that Applicants must set forth a non-exclusive list of highly particularized hybridization conditions including the starting materials, the reaction conditions, the purity of the nucleic acid preparation; base compositions of the probe; length of homologous base sequence; ionic strength; incubation temperature; nucleic acid concentration and incubation time; denaturing reagents; volume exclusion agents; repeated washes or rinses etc. These requirements far exceed the scope of what is claimed.

1. Applicants have invented, describe and claimed a device for carrying out hybridization reactions and are not required to enumerate the infinite permutations of specific biopolymers that can be subjected to hybridization assays or to enumerate the infinite permutations of experimental conditions under which a given researcher may wish to use this utility device in aid of his/her experimental pursuits.

As stated in Applicant's response to the Office Action prior, the term "hybridization" has a clear, definite and unmistakable connotation in the Biochemical arts and applies to biopolymers. In its broadest sense, hybridization refers to the act or process of forming a macromolecular hybrid. One of skill in the art knows that not all biopolymers are hybridizable and indeed, the idea of conducting hybridization assays is to ascertain the degree of hybridizability of a probe sequence or molecule with a complimentary sequence or macromolecule to the extent that it exists in a given sample. Hybridization itself being the test of ascertaining the degree of affinity between macromolecules or macromolecules and

their ligands, based on complimentarity or such other biochemical affinity between the probe sequences and the macromolecular sequence beings assayed for. The device of the present invention is quite simply an inventive chamber having the utility of a hybridization chamber. The device of the instant invention therefore applies to, and can be used, as the artisan desires for all sorts of hybridizable biopolymer assays and the requirement by the Examiner to specifically describe all of them, even up to the minutiae of their genotypic profile, clearly, if not unreasonably, exceeds the bounds of the law. Furthermore, the Biochemical literature is replete with techniques for immobilizing probes or biopolymers on glass surfaces and a given artisan is free to choose whatever method suits their research and it is clearly not the object of the present invention to circumscribe what uses and for what polymers this invention might be used.

By analogy, Applicants are no more required to describe specific biochemical species or hybridization reaction conditions as is the inventor of a test tube required to describe specific chemical species and reaction conditions. Further, by analogy, Applicants are no more required to describe specific biochemical species or hybridization reaction conditions as is the inventor of a Petri-dish required to describe specific microbial or eukaryotic species and culturing conditions. For that at least, it is asserted that the enablement standards being imposed upon the Applicants far exceed that required at law and it should be withdrawn.

2. The references cited by the Examiner to bolster his alleged non-enablement rejections are not analogous to the present invention.

The Examiner cited Zhang et al., (Bioinformatics, vol 19, No. 1, 2003, page 14), Chan (US 2002/0119455) and Carrico (US Patent 5, 200, 313) as tending to teach the unpredictability of hybridization reactions, thus warranting a higher degree of disclosure. To the extent that these citations are not analogous to what is described and claimed, Applicants, respectfully do not accord them any probative weight with respect to exemplifying the degree of disclosure required of Applicants under the law.

U.S. 2002/0119455 relates to:

> "[N]ew methods and products for analyzing polymers and in particular new methods and products useful for determining the sequence of polymers. ... Using the methods of the invention the entire human genome can be sequenced several orders of magnitude faster than could be accomplished using conventional technology. In addition to sequencing the entire genome, the methods and products of the invention can be used to create

comprehensive and multiple expression maps for developmental and disease processes. Paragraph 0025.

Similarly, US 5, 200, 313 relates to:

"A nucleic acid hybridization assay method ... which eliminates the need to immobilize or label sample nucleic acids and which requires but a single probe element. The present invention provides a method for determining a particular polynucleotide sequence in an appropriate test medium containing single stranded nucleic acids. The test medium is combined with an immobilized or immobilizable polynucleotide probe, comprising at least one single stranded base sequence which is substantially complementary to the sequence to be determined, under conditions favorable to hybridization between the sequence to be determined and the complementary probe sequence. The complementary probe sequence will be selected to be substantially composed of RNA when the sequence to be determined is RNA or DNA, that is, such probe sequence can be selected to be RNA whether the sample sequence of interest is RNA or DNA." Col.2 Lines 64-64; col 3, lines 1-17.

In both of these instances, the invention relates to a distinct biochemical reaction methodology requiring hybridization reactions to be carried out on a routine basis. Whereas the present invention could be used in aid of these biochemical assays based on the current specification which adequately describes how to make and use the utility device claimed, there is no further requirement to detail the chemical and physical particulars of any one of the innumerable biochemical reaction methodologies to which the utility device of the present invention can be put.

3. The degree of enablement of the present invention is legally sufficient and is commensurate with those of other analogous U.S. Patents.

Applicants have undertaken a search of proper analogous U.S. Patents and have not seen evidence that they were subjected to the standard of enablement being imposed upon the current invention by the Examiner.

A search of U.S. Patents granted between 1976 and present, having the words, "hybrization" and "device" in their titles reveals the following:

	PAT. NO.	Title
1	6,946,287	Device for providing a hybridization chamber, and process unit and system for hybridizing nucleic acid samples, proteins, and tissue sections

2	6,733,977	Hybridization device and method
3	6,670,133	Microfluidic device for sequencing by hybridization
4	6,589,740	Method and device for detecting hybridization reaction
5	6,518,022	Method for enhancing the hybridization efficiency of target nucleic acids using a self-addressable, self-assembling microelectronic device
6	6,482,640	Hybridization device, case, support, and label agent
7	6,432,696	Thermal and fluidic cycling device for nucleic acid hybridization
8	6,238,910	Thermal and fluid cycling device for nucleic acid hybridization
9	5,595,908	Piezoelectric device for detection of polynucleotide hybridization
10	5,552,270	Methods of DNA sequencing by hybridization based on optimizing concentration of matrix-bound oligonucleotide and device for carrying out same
11	5,450,206	Process and device for checking the conformity of hybridization balls

For the sake of asserting the legal sufficiency of the enablement standards of the present invention, Applicants have studied the disclosure of U.S. 6,946,287, the full description of which is disclosed below in its entirety.

> FIG. 1 shows a perpendicular longitudinal section through a device **1** according to the present invention according to a first embodiment. This device is used for providing a hybridization chamber **2** for hybridizing nucleic acid samples, proteins, or tissue sections on a slide **3**. Device **1** is implemented so that it is movable in relation to this slide **3** (in this case, pivotable around an axis, cf. FIG. 7A), so that hybridization chamber **2** may be opened and closed by the simplest possible movement. An annular sealing surface **4** is used for sealing hybridization chamber **2** by being applied to a surface **5** of this slide **3**. This sealing surface **4** may be an offset surface of device **1** which lies flat on surface **5** of slide **3** (not shown). However, an annular seal is preferably used as sealing surface **4** (shown here as an O-ring and referred to the following as seal **4**), or a lip seal may, for example, also be used as an alternative to this. The device includes lines **6** for supplying and/or removing media to and/or from hybridization chamber **2**. Such media may be reagents for performing the hybridization reaction, such as washing liquids or buffer solutions, or also inert gases (such as nitrogen) for drying the hybridization products on the slides and/or for blowing out media lines **6',6"**. These supply and/or removal lines **6',6"** for washing media preferably each discharge into an agitation

chamber **11'**,**11**. In addition, the device includes a sealable specimen supply line **7**, through which liquids containing RNA or other specimen liquids may be pipetted in by hand. Specimen supply line **7** is preferably sealed using a plastic plug (not shown). As an alternative to this, an automatic specimen supply line (cf. FIG. 8) may be provided. According to the present invention, device **1** includes a media-separating agitation device **8** for moving liquids in relation to the samples of nucleic acids, proteins, or tissue sections immobilized on surface **5** of slide **3**.

In the first embodiment shown in FIG. 1, agitation device **8** of device **1** includes a membrane **9**. This membrane **9** separates a pressure chamber **10**, which is implemented so it is fillable via one of lines **6** with a pressure fluid, from an agitation chamber **11**, which is connected via an agitation line **12** to hybridization chamber **2**. After the device has achieved thermal equilibrium, a specific volume of RNA specimen liquid has been added, and the specimen supply line is sealed, air or another gas (or even a liquid) is added in pulses via lines **6** to pressure chamber **10** (excess pressure version) or suctioned therefrom (partial vacuum version), so that membrane **9** bends in the same rhythm and correspondingly shrinks and/or enlarges agitation chamber **11**. In this way, the specimen liquid is moved toward one or the other end, where a transverse flow channel **15,15'** is preferably located on surface **14** of device **1** directed toward the inside of hybridization chamber **2**, in the same rhythm as the excess pressure and/or partial vacuum and relaxation in hybridization chamber **2**. On one hand, these transverse flow channels make the transverse distribution of the RNA molecules contained in the specimen solution easier, which causes the specimen liquid and/or the wash liquids to be distributed homogeneously over entire surface **5** in hybridization chamber **2**. On the other hand, transverse flow channels **15,15'** may also be used as a reservoir, so that the oscillating movement of the specimen solution (solid double arrow) generated by agitation device **8**, which is integrated in the device, does not lead to a part of hybridization chamber **2** unintentionally remaining dry. A second agitation chamber **11'**, which is also provided with a membrane **9'**, is preferably connected via a second agitation line **12'** to hybridization chamber **2**. If a pressure surge now presses first membrane **9** into first agitation chamber **11**, this pulse is transmitted via first agitation line **12** to the specimen liquid in hybridization chamber **2**. This liquid yields somewhat toward second agitation line **12'** (and may even partially fill it) and elevates the pressure in second agitation chamber **11'**. Because of this, second membrane **9'** bends upward and is elastically stretched at the same time. As soon as the excess pressure in pressure chamber **10** is reduced, both membranes **9,9'** spring back into their rest position and move the specimen liquid in hybridization chamber **2** in the opposite direction. Through this oscillating movement, a specimen liquid having a minimal volume may be distributed practically homogeneously in the hybridization chamber in less than one minute using device **1** according to the present invention.

FIG. 2 shows a horizontal projection of the device from FIG. 1, seen from below. O-ring seal **4** laterally delimits hybridization chamber **2**, which has transverse flow channels **15,15'**, provided as depressions in surface **14** of device **1**, on each of its opposing ends. Slide **3** (in this case a glass slide for

light microscopy) and its optional grip and/or bar-code field **33** are drawn with dashes. A pressure spring **17** which presses on grip field **33** of slide **3** is also clearly visible. As an alternative to the embodiment shown, multiple pressure springs **17** may also be arranged on one device **1**, these pressure springs **17** able to be distributed around the entire circumference of device **1**. When hybridization chamber **2** is opened, such pressure springs **17** ease the automatic separation of slide **3** from device **1**. The alignment of lines **6,6',6"** and the arrangement of agitation chambers **11,11'** and specimen supply line **7** are also visible. All agitation lines **12,12'** and the specimen supply line discharge into transverse flow channels **15,15'**. All lines **6,6',6"** for supplying and/or removing media preferably discharge into a joint connection plane **16**, which is arranged essentially parallel to hybridization chamber **2**. In this case, the discharge openings may be arranged, as shown, offset to one another or on a line running transverse to device **1** (not shown). Recesses (blank arrows) reduce the heat flow to or from device **1**.

FIG. 3 shows a perpendicular longitudinal section through a device **1** according to the present invention according to a second embodiment. Agitation device **8** is implemented here as a membrane pump and includes flow-limiting means **13**, which allow a preferred flow direction (filled arrows) of the liquids moved. Such flow-limiting means **13** may include return valves having balls (shown in FIG. **3**), membranes, etc. and are known per se. A second and third agitation chamber **11',11"**, which are provided with membranes **9',9"**, are preferably connected via a second and/or third agitation line **12',12"** to hybridization chamber **2**. If a pressure surge now pushes first membrane **9** into first agitation chamber **11**, this pulse (thanks to flow-limiting means **13**) is only transmitted to the specimen liquid in hybridization chamber **2** via first and second agitation line **12,12'**. This liquid yields somewhat toward third agitation line **12"**, fills it, and flows back into first agitation chamber **11** via third agitation chamber **11"**. Membranes **9',9"** in agitation chambers **11',11"** are somewhat deformed during each pressure surge and thus have a damping effect, so that particularly careful movement of the specimen liquid in hybridization chamber **2** results. As soon as the excess pressure in pressure chamber **10** abates, membrane **9** springs back into its rest position. This springing back is preferably supported by a partial vacuum which pulsates in diametrical opposition to the pressure surges and is applied to line **6**. Through this flow movement in a closed loop, a specimen liquid having a slightly increased volume may be distributed practically homogeneously and particularly carefully in the hybridization chamber in less than a minute using device **1** according to the present invention.

FIG. 4 shows a horizontal projection of the device from FIG. 3, seen from below. O-ring seal **4** laterally delimits hybridization chamber **2**, which has transverse flow channels **15,15'**, which are provided as depressions in surface **14** of device **1**, on each of its opposing ends. Slide **3** (in this case a glass slide for light microscopy) and its grip field **33** are drawn with dashes. Pressure spring **17**, which presses on grip field **33** of slide **3**, is also clearly visible. When hybridization chamber **2** is opened, this pressure spring **17** eases the automatic separation of slide **3** from device **1**. The alignment of lines **6,6',6"** and the arrangement of agitation chambers **11,11',11"** and specimen supply

line **7** are also visible. Agitation lines **12',12"** and specimen supply line **7** discharge into transverse flow channels **15,15'**. All lines **6,6',6"** for supplying and/or removing media preferably discharge into a joint connection plane **16**, which is arranged essentially parallel to hybridization chamber **2**. In this case, the discharge openings may be arranged offset to one another, as shown, or on a line running transverse to device **1** (not shown). Recesses (blank arrows) reduce the heat flow to or from device **1**.

FIG. 5 shows a three-dimensional view of a frame **21** for carrying four slides **3**, with one slide **3** inserted. Frame **21** includes lengthwise walls **24**, transverse walls **25**, and intermediate walls **26** running essentially parallel to transverse walls **25**. These walls **24,25,26** enclose openings **27** which completely penetrate frame **21**. At the same time, lengthwise walls **24** and/or transverse walls **25** and/or intermediate walls **26** have a shoulder **28** on which slide **3** may be at least partially laid. Frame **21** preferably has an external surface profile and stacking surface profile corresponding to a microplate and includes at least one spring element **29** and one stop **30** for each slide **3** to elastically hold slide **3** inserted into frame **21**.

This frame **21** is a holding device for at least one carrier—particularly for an essentially plate-shaped slide **3**—which includes materials such as glass, plastic, silicon, pyrolytic graphite, and/or metal. Frame **21** preferably has gripping surfaces on its external surface profile defined by lengthwise walls **24** and transverse walls **25** to be engaged by a robot, which may have a gripper of this robot applied to them. Frame **21** is therefore implemented as a slide adapter for microplate systems and has an external surface profile which essentially corresponds to the external surface profile of a microplate. Therefore, such a frame **21**, which additionally has a corresponding stacking surface profile, may be used for placement in a microplate station of a sample analysis and/or sample processing and/or sample storage system. Slide **3**, which is preferably inserted by hand into frame **21**, has at least one spring element **29** applied to it, which is implemented to exercise an elastic force on this slide **3**. This elastic force is essentially aligned in the direction parallel and/or perpendicular to surface **5** of slide **3** and presses this slide **3** against a stop **30**. For simpler insertion and/or removal of slide **3**, frame **21** has grip openings **31**. Every slide **3** inserted is securely held in frame **21** and no longer has to be touched by hand during the entire further method, as is described in International Application CH02/00012, whose priority is based on this frame **21**, to which reference is expressly made here, and which's entire disclosure is incorporated by reference as well as the disclosure of the Swiss Priority Applications CH 0969/01 and CH 0668/02. Frame **21** is preferably produced from plastic in one piece together with spring elements **29** and stops **30** in the injection molding method. DNA samples, preferably arranged in a two-dimensional grid and/or in an array, which are adsorbed on surface **5** of slide **3**, are preferably immobilized on slide **3**. An optional grip field **33**, which is preferably marked, may be touched with the fingers. Very generally, such a field may be implemented as a grip and/or barcode field. If barcodes are used on slides **3**, systems **38** are preferably used which include a barcode reading device. Such a barcode or grip field **33** may also be left out completely or reduced in size so that a larger surface **5** of slide **3** is available to receive the

samples, such as nucleic acid samples (e.g., DNA microarrays), proteins, or tissue sections. In such cases, a device **1** is, of course, selected in which the hybridization chamber **2** defined by sealing surface and/or seal **4** is enlarged.

FIG. 6A shows a horizontal projection of a small system **38** for hybridizing nucleic acid samples, proteins, or tissue sections having a small process unit **18**. This process unit **18** includes at least one device **1**, already described, for providing a hybridization chamber **2**. Such a process unit **18** includes a baseplate **35** and preferably one holder **36** having four seats **37**, which is pivotable around an axis and lockable in relation to a baseplate **35**, per group of four **19**, one device **1** being insertable in each of these seats **37**. This insertion is preferably performed manually, the secure seating of device **1** in holder **36** being ensured by snap-in devices known per se (not shown). This system **38** additionally includes a central control device **39**, a monitor **40**, and a receptacle **41**, which communicates with unit lines **23,23',23"** and lines **6,6',6"**, for storing reagents and/or for collecting wastes. As indicated in FIG. 6A, all parts of the system are operatively connected to one another.

FIG. 6B shows a horizontal projection of a large system **38** for hybridizing DNA microarrays having four large process units **18**. These process units **18** include at least one device **1**, already described, for providing a hybridization chamber **2**. Such a process unit **18** includes a baseplate **35** and preferably one holder **36** having four seats **37**, which is pivotable around an axis and lockable in relation to a baseplate **35**, per group of four **19**, one device **1** being insertable in each of these seats **37**. This insertion is preferably performed manually, the secure seating of device **1** in holder **36** being ensured by snap-in devices known per se (not shown). This system **38** additionally includes a central control device **39**, a monitor **40**, and a receptacle **41**, which communicates with unit lines **23,23',23"** and lines **6,6',6"**, for storing reagents and/or for collecting wastes. As indicated in FIG. 6B, all parts of the system are operatively connected to one another.

Functional units **18,39,40** indicated individually in FIG. 6 may alternatively—possibly together with further functional units, such as barcode readers, etc.—be combined and/or installed into a joint housing. At the same time, the number of process units **18** and/or groups of four **19** may be varied practically as desired. A part of these receptacles **41** (preferably four of six) are heated to protect the liquids contained therein from precipitation; a level control in these receptacles makes the automation of systems **38** easier. The processor in each central control device **39** preferably recognizes which process units **18** and/or groups of four **19** are active. The processor is preferably supplied with information which allows system **38** to establish and execute individual hybridization programs for each group of four **19**. If barcode readers are used, central control device **39** and/or its processor is preferably made capable of detecting the position of each individual slide **3**.

FIG. 7A shows a vertical section through a process unit **1** for hybridizing nucleic acid samples, proteins, or tissue sections with holder **36** open. Devices **1** are preferably arranged parallel to one another and in a group of four **19** (cf. FIG. **6**), because this arrangement allows precisely a dimension for a

temperature control plate **20** on which a frame **21** the size of a microplate (cf. FIG. 5) having four slides **3** arranged parallel to one another fits. Each of these groups of four **19** is assigned a temperature control plate **20** connected to a temperature control device. A temperature control plate **20** is implemented to receive a frame **21** carrying four slides **3** flat. Frame **21** includes, as described above, longitudinal walls **24**, transverse walls **25**, and intermediate walls **26** running essentially parallel to transverse walls **25**. These walls enclose openings **27** which completely penetrate frame **21**. Because longitudinal walls **24** and/or transverse walls **25** and/or intermediate walls **26** have a shoulder **28** on which slide **3** may be at least partially laid, a large area of slide **3** remains free, which may come into direct contact with the surface of temperature control plate **20**. Because slide **3** is softly and elastically held in frame **21** and because temperature control plate **20** is implemented in such a way that the frame can be lowered somewhat in relation to it, slide **3** lies directly on the surface of temperature control plate **20**. Each group of four **19** of a process unit **18** includes one holder **36** having four seats **37**, which is pivotable around an axis **34** and lockable in relation to a baseplate **35**, one device **1** being insertable in each of these seats **37**. Each process unit **18** additionally includes a connection plate **22** for tightly connecting unit lines **23,23',23"** to lines **6,6',6"** of devices **1**. O-rings are preferred as seals for these connections (not shown).

FIG. 7B shows a vertical section through a process unit **1** for hybridizing nucleic acid samples, proteins, or tissue sections with holder **36** closed. All four hybridization chambers **2** of this group of four **19** are assigned a temperature control plate **20** connected to a temperature control device. A temperature control plate **20** is implemented to receive a frame **21** carrying four slides **3** flat, as described above. Each group of four **19** of a process unit **18** includes one holder **36** having four seats **37**, which is pivotable around an axis **34** and lockable in relation to a baseplate **35**, one device **1** being insertable in each of these seats **37**. In order to ensure that devices **1** may be placed plane parallel to slides **3**, the holder also has a central articulated joint (not shown) having movability parallel to axis **34**. In order that seals **4** reliably seal hybridization chambers **2**, an additional pressure is exercised on devices **1** via holder **36**, which may be produced via screws, rocker arms, or similar known devices (not shown).

Each process unit **18** additionally includes a connection plate **22** for tightly connecting unit lines **23,23',23"** to lines **6,6',6"** of devices **1**. O-rings are preferred as seals for these connections (not shown).

FIG. 8 shows specimen injection devices according to a first and/or a second embodiment. Such specimen injection devices are preferably provided in place of manual specimen supplies **7** in fully automated systems **38**, in which the specimen injection is also to be performed automatically.

As shown in FIG. 8A, a corresponding device **1** includes a specimen injection device according to a first embodiment having a specimen receiving vessel **42**, a floating ball **43**, a sealing membrane **44**, and a vacuum connection **45**. A specific volume of a specimen solution is pipetted into specimen receiving

vessel **42** without pressure and preferably using a pipettor (not shown), float ball **43** floats on the specimen solution in this case. The specimen solution is introduced into hybridization chambers **2** as soon as sealing membrane **44** is subjected to a partial vacuum via a vacuum connection **45**: this sealing membrane **44** is elastically deformed in such a way that the specimen liquid flows around the transverse end (see arrow). Aeration of the vacuum connection immediately seals this specimen injection device. If essentially the entire volume of the specimen liquid pipetted into specimen receiving vessel **42** is introduced into hybridization chambers **2**, floating ball **43** automatically seals the opening of the specimen injection device so that no air may reach hybridization chamber **2**. A part **46** of specimen receiving vessel **42** is implemented as a valve seat, a soft plastic material being preferred for valve seat **42** or (preferably) for floating ball **43**.

As shown in FIG. 8B, a corresponding device **1** includes a specimen injection device according to a second embodiment having a specimen receiving vessel **42**, a sealing membrane **44**, and a vacuum connection **45**. A specific volume of a specimen solution is pipetted into specimen receiving vessel **42** with pressure and preferably using a pipettor (not shown). For this purpose, specimen receiving vessel **42** is designed in such a way that the inserted pipette tip of the pipettor presses tightly against the inner wall of specimen receiving vessel **42**. The excess pressure generated using the pipettor allows a specific volume of specimen liquid to push into the space between second membrane **48** and constricted specimen receiving vessel **42** against the resistance of first membrane **47**, which presses tightly. The specimen liquid is introduced into hybridization chamber **2** as soon as second membrane **48** is subjected to a partial vacuum via vacuum connection **45**: this second membrane **48** is elastically deformed in such a way that the specimen liquid flows around the transverse end (see dashed arrow). Aeration of the vacuum connection immediately seals this specimen injection device. If essentially the entire volume of the specimen liquid pipetted into specimen receiving vessel **42** is introduced into hybridization chambers **2**, first membrane **47** automatically seals the opening of the specimen injection device so that no air may reach hybridization chamber **2**.

In the specimen injection devices shown in FIGS. 8A and 8B, a slight partial vacuum, which preferably exists for this purpose in hybridization chamber **2**, makes filling hybridization chamber **2** with the specimen liquid easier.

FIG. 9 shows a specimen injection device according to a third embodiment having a two-part valve **49**, during pipetting of the specimen liquid into specimen receiving vessel **42** (cf. FIG. 9A). A first part **50** of this two-part valve **49** is in its lowermost position and seals specimen supply line **7** of device **1**. A preferably defined volume of the specimen liquid flows via pipette tip **51** into chamber **52** between specimen receiving vessel **42** and first valve part **50** via line **54**, the surface of the liquid defining an appropriate level **53** and the excess air escaping via line **54'**.

An excess pressure medium (e.g. nitrogen gas) is introduced into the space between first valve part **50** and annular second valve part **56** via connection

55, which causes second valve part **56**, which has the excess pressure medium applied to it over a larger area, to yield downward (cf. FIG. **9**B), until it touches the specimen liquid and is braked by it. At the same time, lines **54,54'** are automatically closed. The excess pressure, which is still maintained, now causes second valve part **56** to move upward to its final position (cf. FIG. **9**C), due to which specimen supply line **7** opens and the specimen liquid reaches the hybridization chamber. The excess pressure now further causes second valve part **56** to move all the way downward into its final position and therefore to press the specimen liquid out of chamber **52**. The specimen liquid is therefore introduced into hybridization chamber **2** under pressure according to this embodiment of a specimen injection device and in contrast to the two embodiments previously described (cf. FIG. **8**).

This third embodiment just described relates to a specimen injection device preferably conceived as disposable or expendable material, because then reproduction of its original state (cf. FIG. 9A) may be dispensed with. This is preferred above all if device **1** is also intended to be expendable or disposable material and therefore only to be used once.

In order that these procedures may run routinely and as reproducibly as possible, a system **38** includes a pipettor, using which specimen may be dispensed into specimen receiving vessels **42** of devices **1**, and a vacuum device for generating a partial vacuum on sealing membrane **44**. In this case, systems are preferred in which the pipettor and the vacuum device are controllable and/or regulatable via central control device **39**. For better observability of the processes in hybridization chamber **2**, device **1** is preferably produced from an at least partially transparent plastic. Specimens "labeled" with fluorescein are light-sensitive; a cover which is opaque to light is therefore preferably placed on each group of four **19** in order to prevent light reaching the specimens to which fluorescent materials have been added in hybridization chambers **2**.

It should be mentioned that Applicants are citing U.S. 6,946,287, for the sufficiency of the Applicant's enablement requirement and should not be construed as assertion of its validity. To that extent, the specification of U.S. 6,947,287, did not mention the particulars of the biopolymeric species to be hybridized, let alone mention and particular sequence listings of proteins and nucleic acids. There was further no mention of any particularized hybridization conditions including the starting materials, the reaction conditions, the purity of the nucleic acid preparation; base compositions of the probe; length of homologous base sequence; ionic strength; incubation temperature; nucleic acid concentration and incubation time; denaturing reagents; volume exclusion agents; repeated washes or rinses etc. Instead, the description of U.S. 6,947,287 merely described the embodiments of their hybridization device and how it is to be used, said description being at the level of one of skill in the art to

which it pertains.

To the extent that analogous inventions have not being held to any standard of enablement higher than what the inventors of the instant invention have met, it is again asserted that the enablement standards of the present invention are adequate and there is no basis for continuing this ground for rejection. Applicants respectfully ask that it be withdrawn.

Claims 12 – 13 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. The Examiner asserts that the claims fairly encompass any all manners of biopolymers and that the instant specification fails to particularize the exact biopolymeric species to which claims 12 – 13 are applicable, including setting forth a sequence listing for any protein or nucleic acid. Applicants respectfully disagree and hereby traverse as follows.

The foregoing arguments are hereby incorporated by reference. Claims 12 and 13 are directed to a device for carrying out hybridization reactions. One of skill in the art to which it pertains would be able to utilize this device without burdening the Application with the details which the Examiner deems necessary.

In particular, one of ordinary skill in the art appreciates that the hybridization device of the present invention is an improved version of the so-called DNA chips exemplified by US. Patent No. 6,482,640. These devices are already well known and are commercially available and there is no requirement to provide further guidance to a researcher in terms of the exact biochemical species to which this invention can be used; the utility device of the present invention being applicable to all hybridizable biopolymers.

As such, Applicants see no basis for this ground for rejection and respectfully ask that it be withdrawn as well.

Rejection under 35 U.S.C. §112, 2nd paragraph

Claims 3 – 11 stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asserts that the claims are drawn to a device. The Examiner further asserts that a device is "a single entity comprised of various elements wherein the elements have necessary structural connections." The Examiner then

maintains that there is no structural connection between the cap, the cases, the films and the tray of the present invention, and that the claims of the present invention cannot therefore be drawn to a "device" without rendering them indefinite. Applicants respectfully disagree and now traverse.

In prior responses, Applicants had argued that there was no judicially explicated distinction between "Device" and "Kit" and that applicants should not be constrained to recognize U.S.P.T.O's colloquial distinctions between "Device" and "Kit." The Examiner responded that absent a "clear definition" of "device" in the instant specification, that "device" must be given its broadest reasonable interpretation.

Applicants have used the word device in its plain and ordinary connotation in the sense cited by the Examiner as meaning a "thing made for a particular purpose" and hereby assert that the device of the present invention is a thing made for the purposes of hybridizing biopolymers. That much is agreed.

Where Applicants vigorously differ with the Examiner is with the Examiner's metaphysical construction of "device" beyond its plain and ordinary connotation. According to the Examiner, "device" speaks to a structural relationship between the parts of said device whereas "kit" speaks to a set of parts or articles to be used for some particular purpose.

The Examiner is again referred to the above listed patents which share a substantially degree of analogy to the instant invention in terms of relating to a hybridization device. In the first place, none of the above cited eleven patents specifically defined "device" in their specification – nor should such an otherwise commonly understood phraseology be defined. Contrary to the Examiner's metaphysic's being foisted upon the current applicants, the claimed devices of those inventions are not "single-part" devices. Consonant with the usage in the current invention, other inventors speak of device in terms of a thing made for a particular purpose even if the device may be disassembled into various parts. As long as those parts, like the parts of the present invention are structurally assemblable into a "thing made for a particular purpose," the instant inventors fail to see the basis for maintaining this rejection. It is therefore, respectfully requested that it be withdrawn.

In particular, Figure 4 of the present invention shows a perspective view of the "united hybridization device," to use an exact phraseology mentioned in the instant application. That phrase, "united hybridization device" is very much consistent with the generally understood notion that every device contains inter-related parts for "accomplishing a particular purpose." Again, the Examiner is urged to reconsider his understanding of the

word "device" and to withdraw this ground for rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Response is respectfully requested.

Respectfully submitted,

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